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**Objection to the Specification**

The Examiner stated that the specification is newly objected to because there is no sequence identifier for the sequence presented in figure 5.

In response, applicants respectfully traverse the Examiner's above objection. Applicants maintain that the specification does contain a sequence identifier for the sequence listed in figure 5. The specification recites at page 6, lines 18-19, that "the nucleic acid sequence of the EN-RAGE is the sequence shown in Figure 5 (Seq I.D. No. 1)." Accordingly applicants contend that the sequence identifier in the specification obviate the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

**Rejection Under 35 U.S.C. §112, 1<sup>st</sup>, 2<sup>nd</sup> and 35 U.S.C 103(a)**

The Examiner stated that the rejection of claims 49, 51, and 52 under 35 U.S.C. 112, first paragraph, of claims 48, 49, 51, and 52 under 35 U.S.C. 112, second paragraph, and of claims 48, 49, 51, and 52 under 35 U.S.C. 103(a) are maintained of record because these claims have not in fact been canceled.

In response, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove canceled 48-49 and 51-52 without prejudice or disclaimer to applicants' right to pursue the subject matter of these claims in a later-filed application. Accordingly,

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applicants contend that canceled claims 48-49 and 51-52 obviate the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

**Objection Under 37 C.F.R. 1.75(c)**

The Examiner stated that Claim 50 is newly objected to under 37 C.F.R. §1.75(c), as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. The Examiner stated that applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form. The Examiner stated that Claim 50 depends from Claim 47 but encompasses EN-RAGE peptides, which are not within the scope of Claim 47 as amended.

In response, applicants respectfully traverse the Examiner's above objection. Nevertheless, applicants without conceding the correctness of the Examiner's position but to expedite prosecution of the subject application have hereinabove amended claim 50 such that claim 50 no longer recites "EN-RAGE peptide." Applicants contend that amended claim 50 obviates the above objection and respectfully request that the Examiner reconsider and withdraw this ground of objection.

**Rejection Under 35 U.S.C. §112, first paragraph**

The Examiner stated that the rejection of claims 47, 50, and 55-68 under 35 U.S.C. 112, first paragraph as lacking enablement commensurate with the scope of the claims is maintained and newly

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applied to Claims 70-72. The Examiner alleged that these claims still encompass peptides derived from EN-RAGE or sRAGE. The Examiner stated that while claims 70-72 further define the encompassed antibodies, they do not limit the claimed method to one using antibodies. The Examiner alleged that as written, they encompass methods using EN-RAGE and sRAGE peptides. The Examiner alleged that applicant has not provided guidance sufficient for one of skill in the art to make and use such peptides. The Examiner alleged that there is no information as to the regions of either protein that are important for binding that would allow one of skill to devise peptides that would interfere with such binding. The Examiner alleged that no "ligand-binding domains" as claimed in claim 50 are set forth in the specification or provided by the prior art. The Examiner alleged that thus without further guidance as to the structural and functional features of inhibitory peptides, it would require undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

In response, applicants respectfully traverse the Examiner's above objection. Applicants maintain that the specification is enabled. Applicants contend that the structural and functional features of RAGE inhibitory peptides such as EN-RAGE and sRAGE are disclosed and that it would not require undue experimentation for one of skill in the art to make and use the invention as claimed.

Structural and functional features of EN-RAGE

Applicants contend that EN-RAGE is a member of the highly conserved

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S100/Calgranulin superfamily which structure and function were well known to one of skill in the art at the time of the present invention. Accordingly, it would not have required undue experimentation for one of skill in the art to devise inhibitory peptides that would interfere with EN-RAGE/RAGE binding.

In support, applicants attach hereto as Exhibit B a copy of a paper by Hofmann et al. (Cell 97:889-901, 1999), entitled "RAGE Mediates a Novel Proinflammatory Axis: A Central Cell Surface Receptor for S100/Calgranulin Polypeptides" recites that they have characterized "an ~12kDa polypeptide, termed EN-RAGE, which is in the S100/calgranulin family." See page 889, column 2. Further, Hofmann et al. recites that the strong structural and functional homology between members of the S100/calgranulin superfamily "emphasize the likelihood that a range of S100/calgranulin polypeptide ligands engage RAGE." See page 893, column 2. Accordingly, applicants contend that this paper shows that RAGE is a central cell surface receptor for a wide range of S100/calgranulin superfamily members.

In support, applicants further attach hereto as Exhibit C a copy of a paper by Esteban C. Dell'Angelica et al. (J. Biol. Chem. 269:28929-28936, 1994), entitled "Primary Structure and Binding Properties of Calgranulin C, a Novel S100-like Calcium-binding Protein from Pig Granulocytes" which recites that "the function of calmodulin in Ca<sup>2+</sup> signal transduction has been studied extensively, and many target enzymes have been identified," and that "calcium binding to calmodulin induces a conformational change, thus

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exposing hydrophobic sites that are involved in the interaction with target proteins." See page 28929, column 2. The paper further recites that "the fact that other EF-hand calcium binding proteins (such as S100/calgranulin) also expose hydrophobic regions upon calcium binding suggest that **this model may represent a general mechanism for the function of these proteins as  $\text{Ca}^{2+}$  signal mediators.**" [Emphasis added] See page 28929, column 2. Accordingly, applicants contend that this paper shows that  $\text{Ca}^{2+}$  induces conformational changes to highly conserved hydrophobic regulatory domains on EF-hand calcium-binding proteins (i.e. S100/calgranulin superfamily proteins) and mediate its binding to effector molecules.

Accordingly, applicants contend that these papers recite structural and functional domains necessary for binding of S100/Calgranulin superfamily proteins to effector molecules such that one of skill in the art could devise peptides that would interfere with EN-RAGE/RAGE binding.

#### Structural and functional features of sRAGE

Applicants contend that the structure and function of sRAGE, i.e. the extracellular two-thirds of RAGE, was well known to one of skill in the art at the time of the present invention. Accordingly, it would not have required undue experimentation for one of skill in the art to devise inhibitory peptides that would interfere with EN-RAGE/RAGE binding.

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In support, applicants direct the Examiner to a paper by Neeper et al. (1992) disclosed in the specification at page 40, lines 29-32, and cited in the Information Disclosure Statement filed September 25, 2000, entitled "Cloning and Expression of a Cell Surface Receptor for Advanced Glycosylation End Products of Proteins" which recites that RAGE is a "35kDa polypeptide with a unique NH<sub>2</sub>-terminal sequence" and is a "member of the immunoglobulin superfamily of cell surface molecules" which "functions as a cell surface receptor for AGEs." See page 14998, abstract. Further, the paper recites that the mature RAGE protein is comprised of "an extracellular domain of 332 amino acids, a single hydrophobic membrane spanning domain of 19 amino acids, and a carboxyl-terminal domain of 43 amino acids." See page 14998, abstract, and figure 5, hydrophilicity plot of bovine RAGE. Further, Neeper et al. recites that "human and bovine RAGE molecules are ~90% homologous." See page 14998, abstract. Accordingly, the applicants contend that this paper shows that RAGE is a highly conserved cell surface receptor for AGEs with clearly identified structural and functional domains.

In support, applicants further direct the Examiner to a paper by Schmidt et al. (1994), disclosed in the specification at page 40, lines 17-19, and cited in the Information Disclosure Statement filed on September 25, 2000, entitled "Cellular Receptor for Advanced Glycation End Products: Implications for Induction of Oxidant Stress and Cellular Dysfunction in the Pathogenesis of Vascular Lesions" which state that "sRAGE is a form of RAGE composed

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of the extracellular domain" and that sRAGE specifically blocks AGE-RAGE interactions by "blocking access of receptor to ligand." See page 1523, second column and page 1524, first column. Therefore, applicants contend that this paper shows that sRAGE is an extracellular portion of the highly conserved RAGE polypeptide with a known structure which specifically blocks AGE-RAGE interactions.

Accordingly, applicants contend that these papers recite structural and functional domains necessary for the binding of RAGE to ligand such that one of skill in the art could devise peptides that would interfere with EN-RAGE/RAGE binding.

Applicants contend that these comments obviate the above rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

**Rejection Under 35 U.S.C. §112, second paragraph**

The Examiner stated that the rejection of claims 47, 50, and 55-68 under 35 U.S.C. 112, first paragraph, as lacking written description is similarly maintained and newly applied to claims 70-72. The Examiner alleged that no common structural or functional features of molecules inhibiting RAGE/EN-RAGE interaction, including inhibitory peptides are set forth in the specification. The Examiner alleged that no regions or characteristics, such as binding domains, of either protein that would serve to identify a genus of inhibitors are set forth. The Examiner alleged that one

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skilled in the art would not conclude that applicant was in possession of the claimed genus of peptide inhibitors affecting RAGE/EN-RAGE interaction.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that the structural and functional characteristics of a RAGE inhibitor are described in the subject specification.

Written description of the structure and function of EN-RAGE

The specification does not lack written description. The structural and functional characteristics of EN-RAGE are disclosed in the specification such that one of skill in the art would be able to inhibit EN-RAGE/RAGE binding.

The specification identifies the **structure** of EN-RAGE reciting that "the cDNA for bovine EN-RAGE was cloned and deposited with Genbank at Accession No. AF 011757." See page 5, lines 13-15 and figure 5. Further, the specification recites that "the findings demonstrate that RAGE interacts with a molecule with **close homology to calgranulin C.**"[emphasis added] See page 28, lines 26-27. In addition, the specification identifies the **function** of EN-RAGE reciting that "EN-RAGE:RAGE interaction activates cells such as endothelial cells which are importantly involved in the inflammatory response." See page 28, lines 29-31. Further supporting the disclosure of functional domains important for EN-RAGE binding of ligand, applicants direct the Examiner's attention



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to a paper by Esteban C. Dell'Angelica et al. (J. Biol. Chem. 269:28929-28936, 1994), incorporated by reference in the specification at page 43, lines 17-21 and attached hereto as **Exhibit C**, entitled "Primary Structure and Binding Properties of Calgranulin C, a Novel S100-like Calcium-binding Protein from Pig Granulocytes." which recites that "the function of calmodulin in  $\text{Ca}^{2+}$  signal transduction has been studied extensively, and many target enzymes have been identified," and that "calcium binding to calmodulin induces a conformational change, thus exposing **hydrophobic sites** that are **involved in the interaction with target proteins**." [emphasis added] See page 28929, column 2. Dell'Angelica et al. recite that "the fact that other EF-hand calcium binding proteins (such as S100/calgranulin) also expose hydrophobic regions upon calcium binding suggest that **this model may represent a general mechanism for the function of these proteins** as  $\text{Ca}^{2+}$  signal mediators." [Emphasis added] See page 28929, column 2. Therefore, the structural and functional characteristics of EN-RAGE are disclosed in the specification such that one of skill in the art would be bale to inhibit EN-RAGE/RAGE binding. Accordingly, the specification does **not** lack written description.

Written description of the structure and function of sRAGE

The specification does **not** lack written description. The structural and functional characteristics of sRAGE are disclosed in the specification such that one of skill in the art would be able to inhibit EN-RAGE/RAGE binding using sRAGE.

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In support, applicants direct the Examiner to a paper by Neeper et al. (1992) disclosed in the specification at page 40, lines 29-32, and cited in the Information Disclosure Statement filed September 25, 2000, entitled "Cloning and Expression of a Cell Surface Receptor for Advanced Glycosylation End Products of Proteins" which recites that RAGE is a "35kDa polypeptide with a unique NH2-terminal sequence" and is a "member of the immunoglobulin superfamily of cell surface molecules" which "functions as a cell surface receptor for AGEs." See page 14998, abstract. Further, the paper recites that the mature RAGE protein is comprised of "an extracellular domain of 332 amino acids, a single hydrophobic membrane spanning domain of 19 amino acids, and a carboxyl-terminal domain of 43 amino acids." See page 14998, abstract, and figure 5, hydrophilicity plot of bovine RAGE. Further, Neeper et al. recites that "human and bovine RAGE molecules are ~90% homologous." See page 14998, abstract. Accordingly, the applicants contend that this paper shows that RAGE is a highly conserved cell surface receptor for AGEs with clearly identified structural and functional domains.

In support, applicants further direct the Examiner to a paper by Schmidt et al. (1994), disclosed in the specification at page 40, lines 17-19, and cited in the Information Disclosure Statement filed on September 25, 2000, entitled "Cellular Receptor for Advanced Glycation End Products: Implications for Induction of Oxidant Stress and Cellular Dysfunction in the Pathogenesis of Vascular Lesions" which state that "sRAGE is a form of RAGE composed

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of the extracellular domain" and that sRAGE specifically blocks AGE-RAGE interactions by "blocking access of receptor to ligand." See page 1523, second column and page 1524, first column. Therefore, applicants contend that this paper shows that sRAGE is the extracellular portion of the highly conserved RAGE polypeptide with a known structure that specifically inhibits AGE-RAGE interactions. Therefore, the structural and functional characteristics of sRAGE are disclosed in the specification such that one of skill in the art would be able to inhibit EN-RAGE/RAGE binding using sRAGE. Accordingly, the specification does not lack written description.

Applicants contend that these remarks obviate the Examiner's rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

#### **Rejection Under 35 U.S.C. §103**

The Examiner stated that the rejection of claims 47, 50, and 55-68 under 35 U.S.C. §103 is maintained. The Examiner alleged that applicant argues that the prior art does not fairly suggest a role for RAGE in inflammation. The Examiner alleged that Morser et al., in column 4, lines 48-50, clearly teach that AGEs, ligands for RAGE, produce inflammation via receptor-mediated pathways as well as by other means. The Examiner alleged that Morser et al, further teaches, in lines 54-60, that, because of these effects of AGEs, it is valuable to block AGE/RAGE interactions. The Examiner stated that neither Morser et al. nor the other references of record teach

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EN-RAGE. The Examiner alleged that the use of anti-RAGE antibodies and sRAGE to inhibit inflammation, as instantly claimed, does not rely on effects on or by EN-RAGE. The Examiner alleged that sufficient motivation for one of ordinary skill to use sRAGE or anti-RAGE antibodies is provided by Morser et al., since this reference allegedly teaches that RAGE ligands cause inflammation in a receptor-mediated fashion and explicitly states that compositions that act with AGE receptors have therapeutic use.

In response, applicants respectfully traverse the Examiner's above rejection. Applicants contend that Hori et al. (8/95) and Morser et al. (U.S. Patent 4/96) in view of Ritthaler et al. (1995) do not render the presently claimed invention obvious.

Applicants claimed invention is directed to a method for inhibiting inflammation in a subject which comprises administering to the subject a compound selected from the group consisting of: an anti-EN-RAGE antibody or fragment thereof, an anti-RAGE antibody or fragment thereof, and a soluble RAGE polypeptide or fragment thereof, thereby inhibiting inflammation in the subject.

The Examiner points to the alleged teaching of Morser et al. wherein "the presence of AGEs produce a local chronic inflammation, through a number of mechanisms including receptor-mediated pathways." See column 4, lines 48-50. There is no suggestion of the methods for treating inflammation as presently claimed. Further, there are no suggestions in either Hori et al. or

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Ritthaler et al. which compensate for this lack of disclosure of specifically treating inflammation in the subject. Therefore, there is no support for the Examiner's assertion that there is sufficient motivation for one of ordinary skill to use sRAGE or anti-RAGE antibodies provided by Morser et al. for the claimed purposes, i.e. for inhibiting inflammation in a subject which comprises administering to the subject a compound selected from the group consisting of: an anti-EN-RAGE antibody or fragment thereof, an anti-RAGE antibody or fragment thereof, and a soluble RAGE polypeptide or fragment thereof, thereby inhibiting inflammation in the subject. Therefore, for the reasons stated above, Hori et al. (8/95) and Morser et al. (U.S. Patent 4/96) in view of Ritthaler et al. (1995) do not render the presently claimed invention obvious.

Accordingly, applicants contend that these remarks obviate the Examiner's rejection and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

#### Summary

For the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of objection and rejection and earnestly solicit allowance of the now pending claims, i.e. claims 47, 50, 55-68 and 70-72.

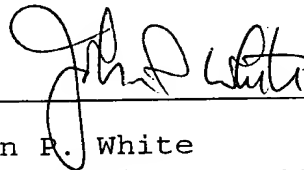
If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number

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provided below.


No fee, other than the enclosed \$460.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

 2/28/02  
John P. White Date  
Reg. No. 28,678